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(54) Title: A MEDICINAL AEROSOL FORMULATION

(57) Abstract: This invention relates to a medicinal aerosol formulation and, more particularly, to a medicinal aerosol formulation containing an insulin combination and a fluid carrier.

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A MEDICINAL AEROSOL FORMULATION

This application claims priority from U.S. provisional application Serial No. 60/177,937 filed January 25, 2000, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a medicinal aerosol formulation for treating diabetes, and more particularly, to a medicinal aerosol formulation comprising a mixture of an insulin or an insulin analog and another β-cell hypoglycemic medicament.

Description of the Related Art

Delivery of drugs to the lung by way of inhalation is an important means of treating a variety of conditions, including such common local conditions as cystic fibrosis, pneumonia, bronchial asthma and chronic obstructive pulmonary disease and some systemic conditions, including hormone replacement, pain management, immune deficiency, erythropoiesis, diabetes, etc. Steroids, β2 agonists, anti-cholinergic agents, proteins and polypeptides are among the drugs that are administered to the lung for such purposes. Such drugs are commonly administered to the lung in the form of an aerosol of particles of respirable size (less than about 10 μm in diameter). The aerosol formulation can be presented as a liquid or a dry powder. In order to assure proper particle size in a liquid aerosol, particles can be prepared in respirable size and then incorporated into a colloidal dispersion either containing a propellant as a pressurized metered dose inhaler (PMDI) or air, such as in the case of a dry powder inhaler (DPI). Alternatively, formulations can be prepared in solution or emulsion form in order to avoid the concern for proper particle size in the formulation. Solution formulations must nevertheless be dispensed in a manner that produces particles or droplets of respirable size.

For MDI application, once prepared, an aerosol formulation is filled into an aerosol canister equipped with a metered dose valve. In the hands of the patient the formulation is dispensed via an actuator adapted to direct the dose from the valve to the patient.

What is needed and desired is a stable aerosol formulation for the treatment of diabetes and the conditions related thereto.

SUMMARY OF THE INVENTION

It has surprisingly been found that a novel and stable medicinal aerosol formulation of an insulin or an insulin analog combined with a β-cell hypoglycemic medicament can be obtained without the use of a surfactant, such as sorbitan trioleate. The selected insulin or insulin analog is combined with another β-cell hypoglycemic medicament, and optionally other diabetic medicaments such as for example the α cell hormone, glucagon.

DETAILED DESCRIPTION OF THE INVENTION

This application makes reference to U.S. Application Serial No. 09/209,228 filed December 10, 1998, which is incorporated hereinto by reference in its entirety.

This invention involves a stable aerosol suspension formulation suitable for pressurized delivery which comprises (a) a particulate insulin combination, and (b) a suitable fluid carrier.

By an "insulin combination" is meant a selected insulin or insulin analog combined with at least one other β-cell hypoglycemic medicament or drug, such as an amylin.

The term "insulin" shall be interpreted to encompass natural extracted human insulin, recombinantly produced human insulin, insulin extracted from bovine and/or porcine sources, recombinantly produced porcine and bovine insulin and mixtures of any of these insulin products. The term is intended to encompass the polypeptide normally used in the treatment of diabetics in a substantially purified form but encompasses the use of the term in its commercially available pharmaceutical form, which includes additional excipients. The insulin is preferably recombinantly produced and may be dehydrated (completely dried) or in solution.

The terms "insulin analog," "monomeric insulin" and the like are used interchangeably herein and are intended to encompass any form of "insulin" as defined above wherein one or more of the amino acids within the polypeptide chain has been replaced with an alternative amino acid and/or wherein one or more of the amino acids has been deleted or wherein one or more additional amino acids has

been added to the polypeptide chain or amino acid sequences which act as insulin in decreasing blood glucose levels. In general, the "insulin analogs" of the present invention include "insulin lispro analogs," as disclosed in U.S. Pat. No. 5,547,929, incorporated hereinto in its entirety by reference, insulin analogs including LysPro insulin and humalog insulin, and other "super insulin analogs", wherein the ability of the insulin analog to affect serum glucose levels is substantially enhanced as compared with conventional insulin as well as hepatoselective insulin analogs which are more active in the liver than in adipose tissue. Preferred analogs are monomeric insulin analogs, which are insulin-like compounds used for the same general purpose as insulin such as insulin lispro i.e., compounds which are administered to reduce blood glucose levels.

A suitable β-cell hypoglycemic medicament is one selected from an amylin. An "amylin" includes natural human amylin, bovine, porcine, rat, rabbit amylin, as well as synthetic, semi-synthetic or recombinant amylin or amylin analogs including pramlintide and other amylin agonists as disclosed in U.S. Pat. No. 5,686,411, and U.S. Pat. No. 5,854,215, both of which are incorporated hereinto by reference in their entirety.

Combined with the insulin combination, e.g. an insulin plus an amylin, is another diabetic medicament. Typically this other medicament is the α cell hormone glucagon. Other diabetic medicaments which can be employed are acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage, phentolamine, etc.

For purposes of the formulations of this invention, which are intended for inhalation into the lungs, the insulin combination is preferably micronized whereby a therapeutically effective amount or fraction (e.g. ninety percent or move) of the insulin combination is particulate. Typically, the particles have a diameter of less than about 10 microns, and preferably less than about 5 microns, in order that the particles can be inhaled into the respiratory tract and/or lungs.

The particulate insulin combination is present in the inventive formulations in a therapeutically effective amount, that is, an amount such that the drug can be administered as a dispersion, an aerosol, such as topically, or via oral or

nasal inhalation, and cause its desired therapeutic effect, typically preferred with one dose, or through several doses. The particulate insulin combination is administered as an aerosol from a conventional valve, e.g., a metered dose valve, through an aerosol adapter also known as an actuator.

The term "amount" as used herein refers to quantity or to concentration as appropriate to the context. The amount of the insulin combination or formulation that constitutes a therapeutically effective amount varies according to factors such as the potency of the particular insulin or insulin analog and the particular β-cell hypoglycemic medicament or medicaments used, as well as the other diabetic medicaments, if used, the route of administration of the formulation, and the mechanical system used to administer the formulation. A therapeutically effective amount of the insulin combination can be selected by those of ordinary skill in the art with due consideration of such factors. Generally a therapeutically effective amount will be from about 0.001 parts by weight to about 5 parts by weight based on 100 parts by weight of the propellant.

Typically, the insulin combination comprises a selected insulin present in an amount of 0.0001 to about 5 parts by weight of the insulin or insulin analog to about 0.0001 to about 5 parts by weight of the selected β-cell hypoglycemic amylin or mixture thereof e.g. an amylin/insulin mixture. Typically, the mixtures of β-cell hypoglycemic medicaments in their respective ranges could be combined with a glucagon or glucagon analog or other diabetic medicament in a concentration range of about 0.001 to about 10 parts by weight based on 100 parts by weight of the propellant.

A suitable fluid carrier is selected. A suitable fluid includes air, a hydrocarbon, such as n-butane, propane, isopentane, etc., or a propellant. A suitable propellant is any fluorocarbon, e.g. a 1-6 hydrogen containing flurocarbon, such as CHF_2CHF_2, CF_3CH_2F, $CH_2F_2CH_3$ and CF_3CHFCF_3; a perfluorocarbon, e.g. a 1-4 carbon perfluorocarbon, such as CF_3CF_3, $CF_3CF_2CF_3$; or any mixture of the foregoing, having a sufficient vapor pressure to render them effective as propellants. Some typical suitable propellants include conventional chlorofluorocarbon (CFC) propellants such as mixtures of propellants 11, 12 and 114 or a mixture of any of the foregoing propellants. Non-CFC propellants such as 1,1,1,2-tetrafluoroethane

(Propellant 134a), 1,1,1,2,3,3,3-heptafluoropropane (Propellant 227) or mixture thereof are preferred. The propellant is preferably present in an amount sufficient to propel a plurality of the selected doses of drug from an aerosol canister.

Optionally, a suitable stabilizer is selected. A suitable stabilizer is a "water addition". As used herein a "water addition" is an amount of water which (1) is added, either initially with other components of the aerosol formulation, e.g. insulin combination and propellant, or after the other components, e.g. insulin combination, fluid carrier, are combined and processed, (2) is in addition to the water which is always present and which develops during processing and/or storage of the aerosol formulation, i.e. "developed" or "nascent" formulation water, and (3) is present in an amount which further stabilizes medicinal aerosol formulation having nascent formulation water.

An aerosol formulation preferably comprises the water addition in an amount effective to more effectively stabilize the formulation relative to an identical formulation not containing the water addition, i.e. containing only nascent formulation water, such that the insulin combination does not settle, cream or flocculate after agitation so quickly as to prevent reproducible dosing of the insulin combination. Reproducible dosing can be achieved if the formulation retains a substantially uniform drug concentration for about fifteen seconds to five minutes agitation.

The particular amount of the water addition that constitutes an effective amount is dependent upon the particular propellant and on the particular insulin combination used in the formulation. It is therefore not practical to enumerate specific effective amounts for use with specific formulations of the invention, but such amounts can readily be determined by those skilled in the art with due consideration of the factors set forth above. Generally, however, the water addition must be present in a formulation in an amount in excess of the concentration of the nascent formulation water. Such concentration of nascent formulation water typically ranges up to 300 parts by weight per one million parts by weight of the total weight of the aerosol formulation. Accordingly, the water addition in excess of this nascent water concentration typically ranges from about 10 parts by weight to about 5000 parts by weight per one million parts by weight of the

total aerosol formulation weight. Most preferred is that the concentration of the water addition is from about 500 parts by weight to about 5000 parts by weight per one million parts by weight of the total weight of the medicinal aerosol formulation.

It is to be emphasized that this is an amount which exceeds the amount of nascent or developed formulation water. It is also to be stressed that this amount of water addition can be added and initially combined with the other components of the formulation, e.g. an insulin and an amylin and fluid carrier, e.g. 1,1,1,2-tetrahydrofluoroethane, or added to the resultant formulation after these other components have been processed, e.g. prior to or subsequent to storage.

It has surprisingly been found that the formulation of the invention is stable without the necessity of employing a cosolvent, such as ethanol, or surfactants. However, further components, such as conventional lubricants or surfactants, cosolvents, ethanol, etc., can also be present in an aerosol formulation of the invention in suitable amounts readily determined by those skilled in the art. In this regard, reference is made to U.S. Patent No. 5,225,183, which is incorporated by reference hereinto in its entirety. Typically, a co-solvent such as ethanol is added in an amount ranging from 0.5 to 10% by weight of the total weight of the formulation.

A most preferred formulation comprises the insulin combination, the fluid carrier, the ethanol cosolvent and the water addition, for example, an insulin and an amylin medicament, 1,1,1,2-tetrafluoroethane, ethanol and the water addition.

Generally the formulations of the invention can be prepared by combining (i) the selected insulin combination in an amount sufficient to provide a plurality of therapeutically effective doses; (ii) the fluid or propellant in an amount sufficient to propel a plurality of doses e.g. from an aerosol canister; and (iii) optionally, the water addition in an amount effective to further stabilize each of the formulations; and (iv) any further optional components, e.g. ethanol as a cosolvent other diabetic medicaments, e.g. glucagon; and dispersing the components. The components can be dispersed using a conventional mixer or homogenizer, by shaking, or by ultrasonic energy as well as by the use of a beadmill or a microfluidizer. Bulk formulations can be transferred to smaller individual aerosol vials by using valve to valve transfer methods, pressure filling or by using

conventional cold-fill methods. It is not required that a component used in a suspension aerosol formulation be soluble in the fluid carrier, e.g. the propellant. Those that are not sufficiently soluble can be coated onto the drug particles in an appropriate amount and the coated particles can then be incorporated in a formulation as described above.

Aerosol canisters equipped with conventional valves, preferably metered dose valves, can be used to deliver the formulations of the invention. It has been found, however, that selection of appropriate valve assemblies for use with aerosol formulations is dependent upon the particular component and other adjuvants used (if any), on the fluid or propellant, and on the particular insulin combination being used. Conventional neoprene and buna valve rubbers used in metered dose valves for delivering conventional CFC formulations often have less than optimal valve delivery characteristics and ease of operation when used with formulations containing HFC-134a or HFC-227. Therefore certain formulations of the invention are preferably dispensed via a valve assembly wherein the diaphragm is made of a nitrile rubber such as DB-218 (American Gasket and Rubber, Schiller Park, Ill.) or an EPDM rubber such as Vistalon™ (Exxon), Royalene™ (UniRoyal), bunaEP (Bayer). Also suitable are diaphragms fashioned by extrusion, injection molding or compression molding from a thermoplastic elastomeric material such as FLEXOMER™ GERS 1085 NT polyolefin (Union Carbide).

Conventional aerosol canisters, coated or uncoated, anodized or unanodized, e.g., those of aluminum, glass, stainless steel, polyethylene terephthalate, and coated canisters or cans with epon, epoxy, etc., can be used to contain a formulation of the invention.

The formulation of the invention can be delivered to the respiratory tract and/or lung by oral inhalation in order to treat diabetes or a condition related to diabetes, which are susceptible of treatment by inhalation. The formulations of the invention can also be delivered by nasal inhalation in order to treat, e.g., diabetes (systemic), or they can be delivered via oral (e.g., buccal) administration in order to treat, e.g., diabetes.

We claim:

1. A medicinal aerosol formulation, which comprises:

(a) a therapeutically effective amount of an insulin combination; and

(b) a fluid carrier.

2. The formulation as defined in claim 1 wherein said insulin combination comprises

(a) a selected insulin or insulin analog; and

(b) a β-cell hypoglycemic amylin medicament.

3. The formulation as defined in claim 2 wherein said insulin is selected from the group consisting of natural, synthetic, recombinant insulins and a mixture of the foregoing insulins.

4. The formulation as defined in claim 3, wherein said β-cell hypoglycemic medicament is selected from the group consisting of an amylin, an amylin analog or insulin or an insulin analog in combination with glucagon, acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, activin, somatostatin and a mixture of any of the foregoing antidiabetic medicaments.

5. The formulation of as defined in claim 3 wherein the insulin is selected from the group consisting of proinsulin, an insulin lispro analog, humalog insulin, a super insulin analog or a mixture of the foregoing insulins.

6. The formulation as defined in claim 3 wherein said insulin combination comprises an amylin and an insulin selected from the group consisting of lisproinsulin, humalog insulin, hepatoselective insulin, a recombinant insulin, natural insulin or a mixture of any of the foregoing insulins.

7. The formulation as defined in claim 6 wherein said insulin combination is combined with glucagon.

8. The formulation as defined in claim 1 wherein said fluid is selected from the group of propellants consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoroethane or a mixture thereof.

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9. The formulation as defined in claim 1 wherein said fluid is selected from the group of hydrocarbons consisting of n-butane, propane, isopentane and a mixture of the foregoing.

10. The formulation as defined in claim 1 which further comprises a stabilizer comprising a water addition present in an amount which is in addition to nascent formulation water.

11. The formulation as defined in claim 1 which further includes a cosolvent.

12. The formulation as defined in claim 11 where said cosolvent comprises ethanol.

13. A method of preparing a medicinal aerosol formulation according to claim 1, which comprises:

(a) combining (i) said insulin combination in an amount sufficient to provide a plurality of therapeutically effective doses, and (ii) said fluid carrier in an amount sufficient to propel a plurality of said therapeutically effective doses from an aerosol canister; and

(b) dispersing components (i) and (ii).

14. The method as defined in claim 13 wherein the medicinal aerosol formulation further comprises combining in step (a) (iii) a stabilizer in an effective stabilizing amount, and in step (b) dispersing components (i) and (ii) with said (iii) stabilizer.

15. The method as defined in claim 14 wherein the medicinal aerosol formulation further comprises combining in step (a) a cosolvent, and in step (b) dispersing components (i), (ii) and (iii) with said cosolvent.

16. A method as defined in claim 15 wherein said cosolvent is ethanol.

17. A method of treating in a human or animal diabetes or a diabetes related condition capable of treatment by oral or nasal inhalation, which comprises, administering a formulation according to claim 1 to said human or animal by oral or nasal inhalation.

18. A formulation according to claim 1 in an aerosol canister equipped with a metered dose valve.

19. A metered dose inhaler containing a medicinal aerosol formulation, the formulation comprising:

(a) an insulin combination in particulate form in a therapeutically effective amount;

(b) a fluid carrier; and

(c) a stabilizer comprising a water addition which is present in an amount which (1) is in excess of nascent formulation water and (2) stabilizes the formulation to prevent settling, creaming or flocculation for a time sufficient to allow reproducible dosing of the insulin combination after agitation of the formulation.

20. The metered dose inhaler as defined in claim 19 wherein said stabilizer is present in an amount in said excess of about 10 parts by weight to about 5000 parts by weight based on one million parts by total weight of the medicinal aerosol formulation.

21. The metered dose inhaler as defined in claim 19 wherein said insulin combination comprises

(a) a selected insulin or a selected insulin analog; and

(b) a β-cell amylin hypoglycemic or amylin analog.

22. The metered dose inhaler as defined in claim 21 wherein said insulin is selected from the group consisting of natural, synthetic, recombinant monomeric insulin and a mixture of the foregoing insulins.

23. The metered dose inhaler as defined in claim 21 wherein said insulin combination is combined with a diabetic medicament selected from the group consisting of glucagon, acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage, phentolamine and a mixture of the foregoing diabetic medicaments.

24. The metered dose inhaler as defined in claim 21 wherein said insulin combination comprises an insulin select from lispro insulin, humalog insulin, hepatoselective insulin, and monomeric insulin and a mixture of the foregoing.

25. The metered dose inhaler as defined in claim 23 which additionally comprises glucagon.

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26. The metered dose inhaler as defined in claim 21 wherein said amylin β cell hypoglycemic is combined with glucagon.

27. The metered dose inhaler as defined in claim 21 wherein said insulin combination comprises an insulin or insulin analog and a mixture of amylin and glucagon.

28. The metered dose inhaler as defined in claim 21 wherein said carrier is a propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoroethane or a mixture thereof.

29. The metered dose inhaler as defined in claim 21 wherein said carrier is a hydrocarbon selected from n-butane, propane, isopentane and a mixture of any of the foregoing hydrocarbons.

30. The metered dose inhaler as defined in claim 21 wherein said formulation further includes a cosolvent.

31. The metered dose inhaler as defined in claim 29 wherein said cosolvent is ethanol.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/00036

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61L 9/04; A61K 38/28; A61M 11/00

US CL : 424/45; 514/4; 128/200.23

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/43, 44, 45; 514/4, 866; 128/200.14, 200.21, 200.23

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	Database Caplus, Accession Number 132:202537, EVANS et al, Recent Developments and Emerging Therapies for Type 2 Diabetes Mellitus, Drugs R&D. 1999, Vol. 2, No. 2, pages 75-94, see abstract.	1-4, 6 --- 5, 7
X - Y	US 5,952,356 A (IKEDA et al.) 14 September 1999 (14.09.99), see abstract, col. 12, lines 39-68, col. 13, lines 1-58, col. 14 lines 13-68, col. 15, lines, 1-40.	1-4, 6, 10-11, 17 --- 5, 7, 13-16, 18-31
X - Y	US 5,744,123 A (AKEHURST et al.) 28 April 1998 (28.04.98) see abstract, col. 1 lines 15-68, col. 2, lines 1-60, col. 3, lines 3-66, col. 4, lines 13-50, col. 5, lines 1-68, col. 6 lines 1-25.	1, 8-9, 11, 13, 17-18 --- 2-7, 12, 14-16, 19-31
Y,P	US 6,136,294 A (ADJEI et al.) 24 October 2000 (24.10.2000) see entire document.	1, 8-20, 28-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

01 May 2001 (01.05.2001)

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Form PCT/ISA/210 (second sheet) (July 1998)

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INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/US01/00036

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: .

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☒ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BNSDOCID: <WO_____0154742A1_I_>

INTERNATIONAL SEARCH REPORT

international application No.

PCT/US01/00036

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING: This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

☐ Group I, claims 1-12, is drawn to a formulation.
☐ Group II, claims 13-16, is drawn to a method making the formulation of Group I.
☐ Group III, claim 17, is drawn to a method of use for the formulation of Group I.
☐ Group IV, claims 18-31, is drawn to an apparatus to dispense the formulation of Group I.

The inventions listed as Groups I, II, III, and IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature for the following reasons: The common special technical feature of each of these inventions is the formulation of claim 1. However, since the formulation of claim 1 is not novel, a common special technical feature does not exist between the four inventions. Claim 1 describes a formulation comprising the insulin and a fluid carrier, however, this combination is commonly used to treat Type II Diabetes. See: Hale et al. 5,607,691 col.3 lines 57-67, col. 4, lines 1-3, col. 17, lines 42-50 and lines 35-52.

Continuation of B. FIELDS SEARCHED Item3: Data Bases: EAST, WEST, STN, CAPLUS, PATENTS
Search Terms: Insulin, Amylin, Aerosol, MDI, Multidose Inhaler

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